



TITLE: Drug Therapy for Chronic Thromboembolic Pulmonary Hypertension: A Review of the Comparative Clinical Effectiveness

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CONTEXT AND POLICY ISSUES

Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive disease which results from incomplete resolution of the vascular obstruction caused by pulmonary thromboembolism.¹ The incidence of CTEPH is not clearly known due to limited data, though it is estimated that it occurs in between 1% to 4% of patients following acute pulmonary embolism.¹⁻³ Characteristics of the disease include increased pulmonary vascular resistance (PVR), and progressive pulmonary hypertension (PH) resulting from obstruction of the pulmonary vasculature by residual thrombi. Left untreated, CTEPH leads to progression of right ventricular failure and death.⁴ Prognosis for CTEPH is poor and proportional to the degree of PH.⁴ The two-year survival rate among patients with severe CTEPH (pulmonary artery pressure [PAP] > 50 mmHg, non-surgically treated) is less than 20%, and the five-year survival of patients with less severe CTEPH is 32%.² In contrast, patients who receive surgical interventions achieve a three-year survival rate ranging between 53% to 76%.³

Pulmonary endarterectomy (PEA) is the first choice treatment for patients with proximal CTEPH.^{1,4-7} However, PEA is not an option when occlusion occurs in distal vessels not surgically accessible, or when patients have comorbidities that preclude the intervention. Furthermore, access to surgical interventions may be lacking, or patients may simply decline PEA.⁴ A medical intervention may be a viable option in situations where the surgical approach is not feasible. In patients who are eligible for PEA, medical treatment before surgery is not indicated, though some investigators have hypothesized that medical treatment before PEA may be beneficial to a significant proportion of CTEPH patients with hemodynamic instability awaiting the procedure, and may prevent clinical deterioration in patients whose surgery is delayed owing to limited resources for surgery.

Riociguat, a soluble guanylate cyclase stimulator (sGC), is currently the only drug with Health Canada approved indication for the management of inoperable CTEPH or persistent or

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recurrent CTEPH after surgical treatment in adults 18 years or older with PH of World Health Organization (WHO) functional class II or III. The WHO functional class ranges from I to IV, with higher numbers indicating greater functional limitations. Since histopathology studies suggest that CTEPH and primary pulmonary artery hypertension (PAH) share common pathways in their pathophysiology and manifest similar small-vessel changes, vasoactive therapies with evidence of efficacy in PAH are commonly prescribed off-label for CTEPH patients who require medical intervention.⁷ In Canada, specific therapies for PAH include sGC stimulators, endothelin receptor antagonists (ERA), phosphodiesterase-5 inhibitors (PDE-5), and prostacyclin analogues. The objective of this report is to review current evidence of comparative efficacy and safety of monotherapy or combination therapy of medical interventions for patients with CTEPH.

RESEARCH QUESTION

What is the comparative efficacy and safety of monotherapy or combination therapy for patients with chronic thromboembolic pulmonary hypertension?

KEY FINDINGS

In the studies reviewed in this report, riociguat was associated with significant improvement in the 6-minute walk distance (6-MWD), pulmonary vascular resistance (PVR), mean pulmonary-artery pressure (mPAP) and cardiac output. World Health Organization (WHO) functional classes in patients receiving riociguat showed significantly favorable changes at 16 weeks compared to placebo. A systematic review and meta-analysis involving a total of eleven studies of various designs showed that following a three-to-six months therapy with bosentan, patients with inoperable CTEPH as well as patients with persistent or recurrent pulmonary hypertension after pulmonary endarterectomy gained significant improvement in the 6-MWD, cardiac index, PAP, and PVR. Another study found that pretreatment with a combination of bosentan and best standard care (defined as use of anticoagulants with or without diuretics and/or oxygen, if clinically indicated) in CTEPH patients awaiting PEA demonstrated significantly greater improvements in 6-MWD and hemodynamic outcomes compared with best standard care alone. In addition, the pretreatment appeared to confer significant right ventricular (RV) remodeling advantages not observed in patients who received best standard care alone. However, the duration of stay in the intensive care unit or the duration of mechanical ventilation use showed no significant difference between the two groups. Sildenafil, administered orally at 40 mg three times daily for 12 weeks, demonstrated significant improvement in PVR compared with placebo, but improvement in 6-MWD did not reach significance.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, EMBASE, The Cochrane Library (2014, Issue 7), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2004 and August 11, 2014.

Selection Criteria and Methods

One researcher screened titles and abstracts from the literature search, retrieved and examined the full-text publications considered to be of relevance to the review, and made final study selection for this report according to the criteria outlined in Table 1.

Table 1: Selection Criteria

Population	Adults (age ≥ 18 years) with CTEPH, independent of the heart failure (HF) functional class.
Intervention	Monotherapy or combination therapy involving any of the following drugs: riociguat, macitentan, epoprostenol, treprostinil, bosentan, ambrisentan, sildenafil, or tadalafil.
Comparator	Monotherapy or combination therapy involving any of the following drugs: riociguat, macitentan, epoprostenol, treprostinil, bosentan, ambrisentan, sildenafil, tadalafil or placebo.
Outcomes	Six (6) minute walk distance (6MWD), change in hemodynamic measures [e.g. pulmonary artery pressure (PAP)], change in HF functional class, quality of life (QOL), hospitalization, death (all-cause and PAH-related), all adverse events. control; mental health/illness – quality of life (QOL); depression severity index scores
Study Designs	Health Technology Assessments (HTA)/Systematic reviews/Meta-analysis; Randomized controlled trials (RCTs).

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1. In particular, studies that focused on surgical interventions and best standard of care, defined as anticoagulants with or without diuretics and/or oxygen, if clinically indicated, were not included. Studies were also excluded if they were published before 2004, if they were duplicate publications of an already selected study, or if they included in at least one of the selected HTAs or systematic reviews.

Critical Appraisal of Individual Studies

The methodological quality of the systematic review and meta-analysis included in this report was assessed using the AMSTAR instrument,⁸ and the RCTs were appraised using the Downs and Black checklist for measuring study quality.⁹ A numerical score was not calculated; the strengths and limitations of the individual studies have been summarized and presented in tabular form in Appendix 3.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 226 citations of which 15 potentially relevant studies were selected upon screening of titles and abstracts. Grey literature searching identified additional two papers bringing the total pool of potential articles to 17 of which five studies were selected for inclusion in this report. Of these, one study⁵ was a sub-study assessing different outcomes in a subset of patients that completed another randomized controlled trial (RCT).¹ The PRISMA flow chart in Appendix 1 outlines the selection process.

Summary of Study Characteristics

Characteristics of included studies have been summarized in Appendix 2

Country of origin

The systematic review and meta-analysis⁶ included eleven studies from several countries. Of the four RCTs included in this reports, two^{1,5} were from the Netherlands while one each was from Germany⁴ and the United Kingdom.⁷

Study setting

The systematic review⁶ did not specify the settings of the included studies. One trial (the CHEST-1 study),⁴ involved 89 centers but there were no details provided about the settings. Two studies^{1,5} took place at an Academic Medical Center. A fourth RCT⁷ was performed at a Pulmonary Vascular Diseases Unit in a hospital.

Patient population

The systematic review⁶ involved a total of 269 patients. The majority (more than 85%) of the patients had inoperable CTEPH due to distal thromboembolism or to comorbidities,⁶ and nearly 14% of patients complained of persistent and or recurrent PH after PEA. Five of the included studies (n = 164) involved CTEPH patients regardless of whether they had an inoperable condition or were experiencing persistent or recurrent PH post-PEA. Four other studies (n = 54) excluded post-PEA patients. The mean age of participants in the included studies ranged from 46 to 70 years. No further demographic or disease status characteristics were provided.

Participants in the CHEST-1 trial⁴ were adult patients (18 to 80 years, n = 261)) with inoperable CTEPH (72%) or persistent or recurrent PH after PEA (28%), who had a 6-MWD of 150 to 450 m, a PVR of more than 300 dyne • sec • cm⁻⁵, and a mPAP of at least 25 mm Hg. The mean age of the patients was 59 years and they were predominantly white (71%) and female (66%). Most of the patients were in WHO functional class II or III. Patients were excluded if they had received an ERA, prostacyclin analogue, PDE-5 inhibitor, or nitric oxide donor within the 3 months before study entry.⁴

Another study,¹ enrolled patients (n =25) with CTEPH awaiting PEA who had a mPAP greater than 25 mm Hg at rest, New York Heart Association (NYHA) functional class III, and a baseline 6-MWD of between 150 to 500 m. The average age of participants was nearly 66 years, and the majority (72%) were female. Data about race distribution were not provided. Patients were excluded if they were classified in NYHA functional class IV (severe heart failure), and if they had started or stopped any specific therapy for PAH within 1 month before screening. A third study⁵ involved some patients (n = 15) from the previously mentioned study.¹ Thus, the baseline hemodynamic characteristics of patients did not differ between the two studies.^{1,5}

A fourth study⁷ included patients (n =19) with newly diagnosed distal CTEPH and patients with persistent PH longer than 3 months post-PEA surgery. The average age of participants in this study was nearly 55 years and females constituted close to half of the study population. The baseline characteristics in this study seemed considerably numerically different among treatment groups, with some differences reaching the level of significance. Patients were

excluded if they had received any PH-specific therapy or nitrate therapy in the 6 months prior to enrollment, and/or if they had a 6-MWD less than 100 m or greater 450 m.

Interventions and comparators

The systematic review and meta-analysis⁶ included studies that evaluated the efficacy and safety of bosentan (an ERA), in patients with objectively confirmed CTEPH. One of the included studies was a randomized placebo-controlled trial. The other included articles used data from cohort and case-control studies.⁶

In the CHEST-1 study,⁴ patients were randomized in 1:2 ratio to receive placebo or riociguat for a 16-week trial. Riociguat was initiated at a dose 1 mg three times daily and adjusted according to systolic systemic arterial pressure and signs or symptoms of hypotension. The dose reached at the end of week-8, was considered to be the appropriate patient-specific dose, on which the patient remained for additional 8 weeks. The final riociguat doses for the study ranged from 0.5 mg to 2.5 mg three times daily. The majority (98%) of patients who completed the study entered an open-label long-term extension study, CHEST-2. However, discussion of that phase is not included in this report as the study is ongoing, with an expected completion date in 2016.

In two other studies^{1,5} patients awaiting PEA were randomly assigned to receive “best standard of care” (defined as anticoagulants with or without diuretics and/or oxygen, if clinically indicated) with or without bosentan for 16 weeks. Bosentan was prescribed as 62.5 mg twice daily for 4 weeks, followed by 125 mg twice daily for 12 weeks according to standard guidelines; and was stopped in all patients on the day of the PEA operation.

Another study⁷ randomized patients in a 1:1 ratio to receive sildenafil (a PDE-5 inhibitor) at 40 mg or placebo three times daily for a 12-week study

Outcome Measures

In the systematic review,⁶ 6-MWD was the primary outcome in most of the selected studies. The 6-MWD at 3 to 6 months from baseline was reported in nine of the included studies and four studies reported 6-MWD at one year from the start of bosentan therapy. NYHA or WHO functional classes at both baseline and at follow-up were assessed in all studies, except one. Seven studies (n = 185) reported on cardiac index at baseline and at 3 to 6 months follow-up.⁶ Five of the included studies (n = 164) reported on PVR and PAP. All eleven included studies had data on toxicity, with ten of them providing data on mortality in CTEPH patients treated with bosentan.

The primary outcome measure of the CHEST-1 study⁴ was the change from baseline to the end of week 16 in 6-MWD. Secondary endpoints included changes from baseline in PVR, WHO functional class, quality-of-life (QOL) variables, and safety.

In another study,¹ the primary outcome measure was change from baseline in total pulmonary resistance (TPR) after 16 weeks of treatment, while secondary endpoints included change in 6-MWD, mPAP, and cardiac index. In a related sub-study⁵ involving a subset of the population who completed the study, baseline and post-study cardiac magnetic resonance imaging (cMRI) outcomes were used to assess the pulmonary remodeling potential of bosentan. Pulmonary hemodynamics and 6-MWD were evaluated as described in the parent study.^{1,5}

In a fourth study,⁷ the primary outcome measure was the change in 6-MWD from baseline to week-12 and secondary outcome measures included WHO functional status, cardiopulmonary hemodynamic measurements, and QOL as measured by the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR). The CAMPHOR comprises three sections, two of which measure health-related QOL (HRQOL), and one that assesses global QOL.

Summary of Critical Appraisal

Appendix 3 provides further details of the critical appraisal of individual studies

The systematic review⁶ clearly stated objectives and provided well-defined inclusion and exclusion criteria, as well as a list of the included studies with some characteristics, and references to excluded studies. The included studies were selected independently by four reviewers with disagreements resolved by consensus. While the literature searching covered a 12 year period in two electronic databases, there was no indication that a grey literature search was conducted, and whether or not language restrictions were applied. Therefore, it is indeterminate whether a comprehensive literature search was performed. Quality of the studies was reported to have been independently assessed by two reviewers having expertise in research methods, who used appropriate separate tools for the RCT and observational studies. However, the results of the assessment were not reported and the conclusions of the systematic review and meta-analysis made no reference to the methodological rigor and scientific quality of the included studies. Cochrane's Chi square and I^2 tests were used to assess between-study heterogeneity. This was particularly important given the variety of designs of the included studies. A P -value < 0.10 and $I^2 > 50\%$ were considered criteria for statistically significant heterogeneity. The authors did not acknowledge any source of financial support and there was no statement on potential conflict of interest.

The CHEST-1 study⁴ and the other RCTs^{1,5,7} included in this report had clearly described objectives, interventions and comparators, and outcomes of interest. In addition, all the studies clearly described the main study findings and adverse events. The baseline characteristics were well-balanced across treatment groups in all the studies except one,⁷ in which many baseline characteristics seemed considerably numerically different across the treatment groups, with some (WHO functional class, patients who have undergone PEA, and CAMPHOR score in all three domains) reaching the level of significance. Thus for this study,⁷ it is difficult to draw firm conclusions from the observed differences given the potential confounding due to the differences. The study⁵ which investigated the pulmonary remodeling effect of bosentan reported that baseline hemodynamic characteristics between the patients who were included did not differ from the patients who could not be included, suggesting that though only a subset of the originally randomized population participated, the initial randomization effect may have been maintained in this respect.

In the CHEST-1 study⁴ randomization was done using an interactive voice-response system and a computer-generated random code to promote concealment and minimize bias. The study⁴ was sufficiently powered to detect differences in the primary outcome (6-MWD) between treatment groups. However, it is unknown whether it had sufficient power to detect clinically significant differences in hemodynamic and QOL parameters which were secondary outcomes of the study.⁴ Determination of all the outcome measures of the study followed prescribed guidelines, and statistical tests used to assess the outcomes were appropriate. The CHEST-1 study⁴ used the modified intention-to-treat population, which included all randomized patients who received at least one dose of study medication for primary analysis and thus preserved the

randomization effect. The adherence rate was not reported, though data was provided on patients who completed the study. A total of 18 patients (6.9%) withdrew from the study before week 16.⁴ Imputation for missing data applied a multivariate linear model over the “whole longitudinal profiles, with unconstrained time profiles and unstructured covariance matrices.”⁴ According to the investigators, the results of missing data sensitivity analyses did not differ greatly from the results of the primary analysis due to the overall small number of non-completers (13 [8%] in the riociguat group and 5 [6%] in the placebo group), which may be supportive of the rigor of the study.

Details about randomization in the other three RCTs^{1,4,5} were not provided so it is unknown whether assignment to treatment groups were sufficiently random. The baseline characteristics in two of the studies^{1,5} were well-balanced. In another study,⁷ significant differences between the treatment groups were observed with respect to baseline WHO functional status, quality-of-life (as assessed by the CAMPHOR scores), and proportion of post-PEA patients despite randomization. One study¹ reported that it was single-blind, with the patients knowing whether they received bosentan or not, but observers and technical staff performing the tests blinded to the treatment assignment. However, a sub-study in a portion of the patients who completed the trial described it as “randomized, yet open-label.”⁵ Measures taken to reduce potential bias from the open-label design included determination of pulmonary hemodynamic measurements at baseline and at the end of the study (16 weeks) by an observer who was blinded to the treatment regimen. The derivative sub-study⁵ sought to minimize observer bias by making a technician who was unaware of the patients’ treatment regimen perform all cMRI studies in a randomized order, while one treatment-blinded observer analyzed each cMRI parameter to avoid inter-observer variation.

Three studies^{1,5,7} had small sample sizes with none of them calculating the sample size necessary to detect clinically significant differences in any outcomes between their respective treatment groups. Determination of all relevant endpoints of the studies was done according to accepted guidelines and statistical tests used to assess the outcomes were appropriate. Details about adherence rate was not provided in any of the three studies^{1,5,7} though one study¹ reported that all participants completed the study, except one in the bosentan group who had to be withdrawn at 8 weeks of treatment owing to abnormal elevation (6 times the upper limit of normal) in liver enzymes.

The systematic review⁶ did not discuss the exclusion criteria of its included studies. For the RCTs,^{1,4,5,7} their exclusion criteria seemed to eliminate patients with either less severe or very severe CTEPH conditions on the basis of baseline 6-MWD and/or hemodynamic (WHO or NYHA functional) scores. Thus, it is uncertain how the reported findings could be generalized to these patient populations. Moreover, all the studies were performed outside Canada, and so, the generalizability of their findings in this country is uncertain.

Summary of Findings

Five included studies in the systematic review,⁶ which included both inoperable CTEPH patients and those with persistent or recurrent PH post-PEA, reported a weighted mean difference in the 6-MWD after 3 to 6 months of bosentan therapy of 27.6 meters (95% confidence interval [CI]: 24.97 to 30.25 meters). Four included studies in the systematic review, which excluded post-PEA patients, reported a weighted mean difference in the 6-MWD at 3 to 6 months of 64 meters (95% CI: 61 to 67 meters). For the included studies which reported 6-MWD at one year from the start of bosentan therapy, an additional weighted mean increase of 21 meters (95% CI: 18 to 24

meters) in the 6-MWD from 3 to 6 months up to one year was observed, with the absolute values ranging from 0 to 57 meters.⁶

In five of the included studies in the systematic review,⁶ the weighted mean reduction in PVR after 3 to 6 months of bosentan therapy was $-159.7 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$ (95% CI: -153.94 to -165.51), with a mean weighted decrease in PAP of 2.62 mm Hg (95% CI: 2.44 to 2.80 mm Hg). The reduction in PVR and PAP were about 20% and 6%, respectively, of the baseline values. Seven of the included studies in the systematic review reported on cardiac index with the weighted mean increase at 3 to 6 months of 0.23 l/min/m^2 (95% CI: 0.22 to 0.25; $P < 0.001$). The reported weighted mean changes in PVR, PAP, and cardiac index were similar between studies regardless of whether patients with persistent or recurrent PH post-PEA were included or not.

The most common adverse events reported in the systematic review⁶ related to liver function and significant transaminase increase. Progressive worsening of right heart failure with severe fluid retention was reported in one patient. Three patients died within 3 to 6 months, three more died within one year, and an additional three died after 24 months of starting bosentan therapy. Causes of death included progression of renal cells carcinoma, fever, refractory right heart failure, arrhythmia, and PH progression.

In the CHEST-1 study,⁴ the 6-MWD showed a mean increase of 39 meters from baseline in the riociguat group at week 16 compared with a mean decrease of 6 meters in the placebo group (least-squares mean difference, 46 meters; 95% CI: 25 to 67; $P < 0.001$). Pulmonary vascular resistance decreased by $226 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$ in the riociguat group and increased by $23 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$ in the placebo group (least-squares mean difference, $-246 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$; 95% CI, -303 to -190 ; $P < 0.001$). Riociguat was also associated with significant improvement in other hemodynamic variables, including mPAP and cardiac output, and the WHO functional classes in patients receiving riociguat showed significantly favorable changes at 16 weeks compared with those who received placebo.⁴ In terms of QOL, patients in the riociguat group reported a significantly higher EQ-5D score than the placebo group, though the QOL data were considered exploratory.⁴

The most common serious adverse events in the CHEST-1 study⁴ were right ventricular failure (in 3% of patients in each group) and syncope (in 2% of the riociguat group and in 3% of the placebo group). Deaths related to adverse events occurred in two patients (1%) in the riociguat group (one each with heart failure and acute renal failure) and in three patients (3%) in the placebo group (one each with respiratory insufficiency, circulatory arrest, and cardiac arrest).⁴

In another study,¹ patients awaiting PEA who were treated with bosentan demonstrated a significant increase in 6-MWD (348 ± 86 to 379 ± 90 meters; $P = 0.003$) compared to patients in the no-bosentan group (i.e. receiving best standard care alone) who did not show significant change in 6-MWD (391 ± 87 to 388 ± 95 meters; $P = 0.79$) after 16 weeks. The mean difference in change in 6-MWD between the two groups was 33 meters (95% CI: 7 to 59 m; $P = 0.01$). Hemodynamic improvements were reported in patients in the bosentan group whereas no differences were observed in the no-bosentan group. The mean difference in the changes in TPR between bosentan-treated and no-bosentan groups after 16 weeks of treatment was $299 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$ (95% CI: 105 to 493; $P = 0.004$).¹ The mean difference between the observed changes from baseline in mPAP was 11 mm Hg (95% CI: 4 to 19 mm Hg; $P = 0.005$).¹ Patients who were pretreated with bosentan also tended to have a better hemodynamic outcome after PEA than those in the no-bosentan group, although the differences did not reach statistical

significance ($P = 0.09$ for mPAP, and $P = 0.08$ for TRP).¹ Short-term postoperative duration of stay in the intensive care unit or the duration of mechanical ventilation use showed no significant difference between the two groups.

In the same study,¹ the completion rate was high with only one patient in the bosentan group withdrawn at 8 weeks of treatment owing to abnormal elevation (6 times the upper limit of normal) in liver enzymes. The enzyme levels normalized after bosentan treatment was stopped. All the participants in the no-bosentan completed the study. One patient treated with bosentan died post-PEA due to sepsis of pulmonary origin with subsequent multi-organ failure.¹ Three patients from the no-bosentan group died; one of them during surgery as a result of massive alveolar hemorrhage, and two died post-PEA due to progressive right heart failure.¹

A sub-study⁵ which used cMRI to investigate the remodeling effect of bosentan in a subset of patients from the previously described RCT,¹ reported a small increase from baseline in right ventricular (RV) and left ventricular (LV) systolic function in the bosentan group in contrast to the no-bosentan group where a worsening of the systolic function was observed. Thus, the change from baseline in all systolic-function parameters differed significantly between patients in the two treatment groups. Furthermore, whereas RV mass decreased significantly in the bosentan group, RV mass increased in the no-bosentan group. In addition, left ventricular septal bowing (LVSB) improved and RV end-systolic volume decreased in the bosentan treated group. There was a statistically significant difference between the treatment groups in terms of change from baseline mPAP (-11 mm Hg [95% CI: -17 to -11] compared with 5 mm Hg [95% CI: -6 to -21], $P < 0.05$).⁵ Thus, RV remodeling differed significantly in favor of the bosentan group as determined by these parameters.

In another study,⁷ distal CTEPH patients showed improvements in 6-MWD after sildenafil treatment for 12 weeks, though the difference did not reach statistical significance. Statistically significant improvements in PVR and WHO functional class were observed in the sildenafil group compared to the control at 12 weeks.⁷ The improvement in PVR reportedly remained significant even after results were adjusted for baseline differences.⁷ However, it was not reported whether the same applied to the WHO functional class which had significant baseline disparities similar to the PVR.

Patients in the sildenafil group achieved improvements in mPAP compared to those who received placebo.⁷ Though the change in mPAP within the sildenafil group at week-12 compared with baseline was also statistically significant (-6.5 mm Hg; 95% CI: -12.0 to -1.1 ; $P = 0.026$), the difference in mPAP between treatment groups did not reach significance in the intention-to-treat analysis (-6.2 mm Hg; 95% CI: -12.4 to 0.1 ; $P = 0.052$).⁷ Only the activity component of the CAMPHOR score showed a significant improvement among patients receiving sildenafil (-2.9 ; 95% CI, -4.7 to -1.0 ; $P = 0.008$). However, it is difficult to draw conclusions from the comparison of the two groups since a higher proportion of the placebo group had already received a PEA intervention that could influence patients' perceived QOL.

In this study,⁷ the most commonly reported adverse event was extensive urticarial rash in the sildenafil group, which resolved rapidly after the medication was withdrawn. Dyspepsia and headache occurred in both treatments groups, though more with sildenafil than with placebo.⁷

Limitations

Important limitations of this report include the fact that the literature search produced studies involving only two of the PAH drugs (bosentan and sildenafil) that may be used off-label for the management of CTEPH. The search found no studies on any drug from the prostacyclin analogues class that could be included in this report. Furthermore, none of the studies had a direct active comparator and there was no indirect comparison study to allow any comparative efficacy and safety inferences to be made.

The combination of studies with different designs – single-arm cohort studies, RCT, case-control study, and a case report – introduced limitations due to heterogeneity in the systematic review and meta-analysis.⁶ In addition, many of the included studies had small sample sizes (n ranging from 1 to 77, with n > 20 in only three studies) raising questions about how adequately they were powered to detect relevance differences. Coupled with concerns about power is the fact that the authors did not provide any information about the quality of the individual included studies, and the conclusions of the systematic review and meta-analysis⁶ were not explicitly linked to the methodological rigor and scientific quality of the included studies.

While the CHEST-1 study⁴ which investigated riociguat in inoperable CTEPH patients and post-PEA patient with persistent or recurrent PH was generally of high quality, lack of follow-up efficacy measurements in patients who withdrew from the study was a limitation. However, the authors reported that sensitivity analyses suggested that the reliability of the study findings was not diminished by losses to follow-up.⁴ The other RCTs^{1,5,7} had small sample sizes and the numbers required to detect a difference within the outcome measures were not predetermined. As such, they may have been inadequately powered to prevent type II errors. Two of the studies^{1,5} were inadequately blinded which may have influenced results of the 6-MWD tests in patients who were aware of the intervention they were receiving and thus, may have been motivated to improve their efforts. For another study,⁷ there were disparities between the treatment groups at baseline which may have confounded its results.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The systematic review and meta-analysis showed that bosentan therapy is associated with an improvement of hemodynamics and 6-MWD in patients with CTEPH. The CHEST-1 study⁴ found significantly improved 6-MWD and PVR in patients with CTEPH who were treated with riociguat compared with placebo. Though, preoperative treatment with the oral bosentan was shown to significantly improve hemodynamics, functional improvement (6-MWD), and pulmonary remodeling potential in proximal CTEPH patients awaiting PEA, there was no evidence that preoperative treatment with bosentan improved morbidity or mortality outcomes associated with PEA. The study involving sildenafil suggested beneficial effects in favor of sildenafil in several secondary endpoints. Of the four RCTs included in this report, only the CHEST-1 trial was sufficiently powered to permit a substantive conclusion to be drawn from its findings. Considering the quality and limitations of studies included in this report, evidence-based conclusions could not be drawn concerning the comparative efficacy and safety of the drugs covered in it for patients with CTEPH, whether as monotherapy or combination therapy.

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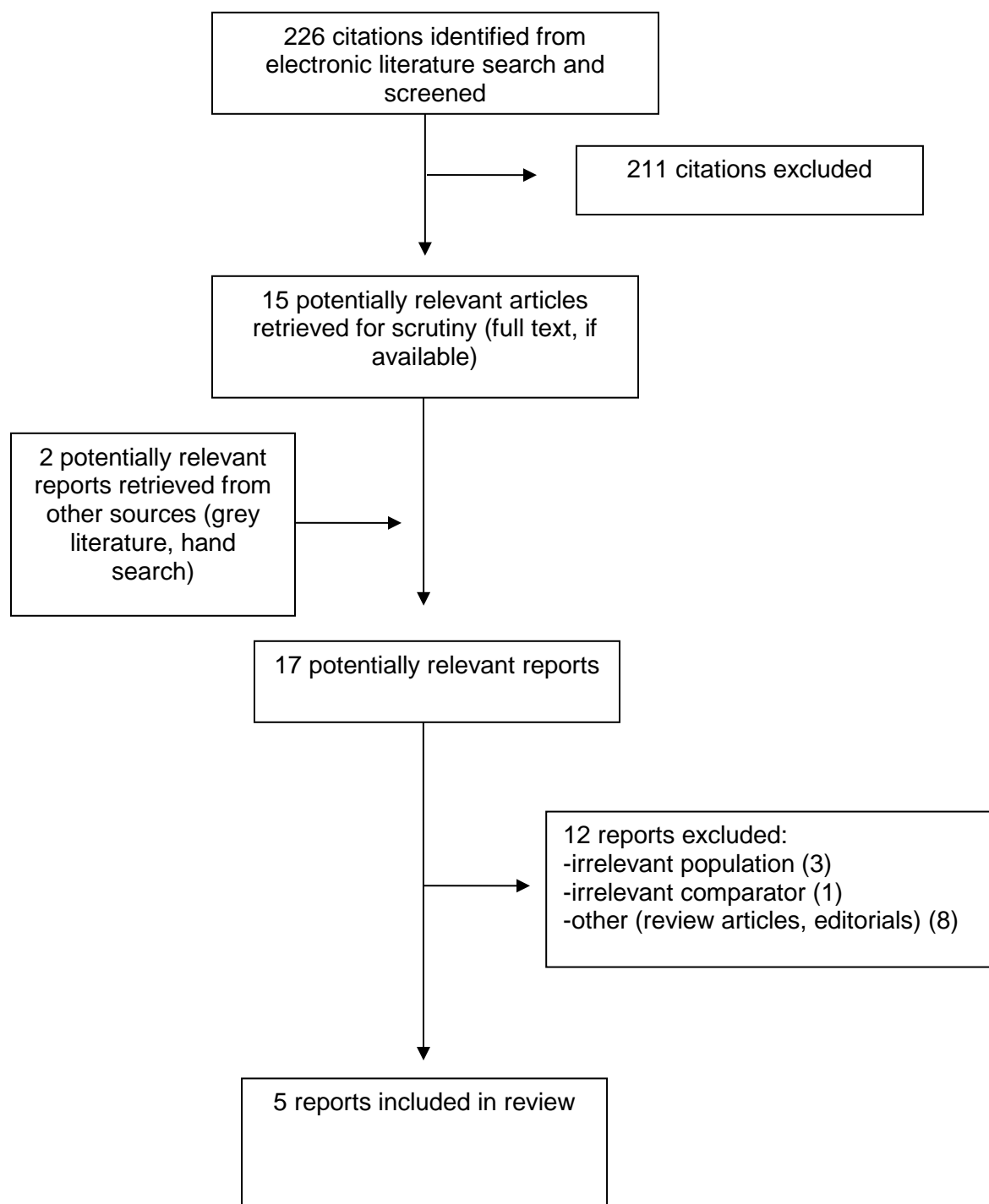
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REFERENCES

1. Reesink HJ, Surie S, Kloek JJ, Tan HL, Tepaske R, Fedullo PF, et al. Bosentan as a bridge to pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *J Thorac Cardiovasc Surg*. 2010 Jan;139(1):85-91.
2. Mehta S. Chronic thromboembolic PH: recognition and management of the most important type of PH [Internet]. Poster presented at: Canadian Respiratory Conference 2012. 2012 Apr 28; Vancouver (BC). [cited 2014 Sep 5]. Available from: <http://www.lung.ca/crc/2012presentations/Mehta.pdf>
3. Helmersen D. Chronic thromboembolic pulmonary hypertension: improving care in Canada [Internet]. Poster presented at: Canadian Respiratory Conference 2013. 2013 Apr 11; Quebec City (QC). [cited 2014 Sep 8]. Available from: http://www.lung.ca/crc/pdf/2013/Helmerson_D.pdf
4. Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med* [Internet]. 2013 Jul 25 [cited 2014 Aug 15];369(4):319-29. Available from: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1209657>
5. Surie S, Reesink HJ, Marcus JT, van der Plas MN, Kloek JJ, Vonk-Noordegraaf A, et al. Bosentan treatment is associated with improvement of right ventricular function and remodeling in chronic thromboembolic pulmonary hypertension. *Clin Cardiol*. 2013 Nov;36(11):698-703.
6. Becattini C, Manina G, Busti C, Gennarini S, Agnelli G. Bosentan for chronic thromboembolic pulmonary hypertension: findings from a systematic review and meta-analysis. *Thromb Res*. 2010 Jul;126(1):e51-e56.
7. Suntharalingam J, Treacy CM, Doughty NJ, Goldsmith K, Soon E, Toshner MR, et al. Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension. *Chest*. 2008 Aug [cited 2014 Aug 15];134(2):229-36. Available from: <http://journal.publications.chestnet.org/data/Journals/CHEST/22075/zcb00808000229.pdf>
8. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* [Internet]. 2007 [cited 2014 Sep 9];7:10. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf>
9. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* [Internet]. 1998 Jun [cited 2014 Sep 9];52(6):377-84. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf>

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

First Author, Publication year, Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcome*
Becattini, ⁶ 2010 Italy	SR/MA	Patients (n = 269) with inoperable CTEPH due to distal thromboembolism or to comorbidities, as well as patients who complained of persistent and or recurrent PH after PEA. Patients' mean age ranged from 46 to 70 years	Bosentan	Placebo	<u>Primary:</u> Changes from baseline in 6-MWD and NYHA class, <u>Secondary:</u> Changes in mPAP, cardiac index, and PVR
Ghofrani, ⁴ 2013 Germany	RCT	Patients (n = 261) with inoperable CTEPH or persistent or recurrent PH after PEA, with a 6-MWD of 150 to 450 m, PVR of more than 300 dyne • sec • cm ⁻⁵ , and a mPAP of at least 25 mm Hg. Mean age of participants was 59 years in the two treatment groups.	Riociguat	Placebo	<u>Primary:</u> Change from baseline in 6-MWD at 16 weeks. <u>Secondary:</u> changes from baseline in PVR, WHO functional class, HRQOL, and safety
Reesink, ¹ 2010 The Netherlands	RCT	Patients (n = 25) diagnosed with surgically accessible proximal CTEPH, with mPAP greater than 25 mm Hg at rest, and baseline 6-MWD of 150 to 500 meters, who were waiting for PEA. The mean age of patients was 67 ± 8 and 64 ± 10 years in the bosentan and the no-bosentan groups, respectively.	Bosentan plus Best standard care ^a	No-Bosentan (Best standard care alone)	<u>Primary:</u> Change from baseline in total pulmonary resistance (TPR) after 16 weeks. <u>Secondary:</u> Change in 6-MWD, mPAP, and safety.
Suntharalingam, ⁷ 2008 United Kingdom	RCT	Newly-diagnosed distal CTEPH patients (n = 19) and patients with persistent and or recurrent PH more than 3 months after PEA. The baseline PVR was 814 ± 385 and 654 ± 342 dyne • sec • cm ⁻⁵ in the sildenafil and placebo groups, respectively, while mPAP had corresponding baseline values of 45.8 ± 8.0 and 42.7 ± 10.1 for the two groups. The mean age of patients was 49.9 ± 13.1 and 60.0 ± 14.4 years in the sildenafil and the placebo groups, respectively.	Oral sildenafil at 40 mg TID	Placebo at two tablets TID	<u>Primary:</u> Change in 6-MWD from baseline to week 12. <u>Secondary:</u> WHO functional status, cardiopulmonary hemodynamic measurements, HRQOL
Surie, ⁵ 2013	RCT	Patients (n = 15) diagnosed with surgically accessible proximal CTEPH, with mPAP greater than 25 mm Hg at rest, and baseline 6-	Bosentan plus	No-Bosentan (Best	Changes from baseline in pulmonary remodeling

First Author, Publication year, Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcome*
The Netherlands		MWD of 150 to 500 meters, who were waiting for PEA. The mean age of patients was 71 (range: 51 to 78) and 65 (range: 56 to 78) years in the bosentan and the no-bosentan groups, respectively.	Best standard care ^a	standard care alone)	parameters as determined by cMRI
6-MWD = 6 minute walking distance; cMRI = cardiac magnetic resonance imaging; CTEPH = chronic thromboembolic pulmonary hypertension; HRQOL = health related quality of life; MA = meta-analysis; NYHA = New York Heart Association; mPAP = mean pulmonary artery pressure; PEA = pulmonary endarterectomy; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; TPR = total pulmonary resistance; RCT = randomized controlled trial; SR = systematic review; TID = three times daily WHO = World Health Organization					

*Only outcomes relevant to this report have been included

^a Best Standard care was defined as anticoagulants with or without diuretics and/or oxygen, if clinically indicated.^{1,5}

Appendix 3: Summary of Critical Appraisal if Included Studies

First Author, Publication year	Strengths	Limitations
Becattini, ⁶ 2010	<ol style="list-style-type: none"> 1. The titles and abstracts of all articles were independently evaluated by 4 reviewers who also independently selected final included articles, resolving disagreements by consensus. 2. Study quality was independently assessed by 2 reviewers having expertise in research methods. 	<ol style="list-style-type: none"> 1. Significant heterogeneity in included studies consisting predominantly of cohort studies (n=8) together with one each of RCT and case control studies. 2. Improvement in exercise capacity seems mainly driven by the results of open-label studies without confirmation in the included RCT, in which a trend towards a mild reduction of 6-MWD in patients randomized to placebo was observed.
Ghofrani, ⁴ 2013	<ol style="list-style-type: none"> 1. The characteristics of the patients at baseline were well balanced between the two groups 2. The study was sufficiently powered to detect difference from baseline in the primary outcome. 3. Efficacy analysis was performed with data from modified ITT with missing data imputed appropriately so that randomization effect was preserved. 	<ol style="list-style-type: none"> 1. Patients who withdrew from the study were not followed-up for efficacy measurements. However, sensitivity analyses that used a variety of approaches to impute missing data suggest that the results are reliable, despite losses to follow-up. 2. With so many study centers (89) and several countries (26) involved with the study, it is unclear how much inter-observer variations may have affected the reported outcomes.
Reesink, ¹ 2010	<ol style="list-style-type: none"> 1. Baseline clinical and hemodynamic characteristics were similar between the groups with no statistically significant differences 2. Possible observer bias was minimized by blinding all observers toward the treatment regimen. 	<ol style="list-style-type: none"> 1. Being an open-label study, patients who knew they received an active treatment were more likely to perceive improvement and therefore made greater effort to improve their 6-MWD. 2. Selection of patients on the basis of 6-MWD may have excluded younger patients who walked relatively long distances and included older patients whose 6-MWD was in part limited by age-related physical conditions unrelated to CTEPH.
Suntharalingam, ⁷ 2008	<ol style="list-style-type: none"> 1. For the randomized-controlled phase of the study, ITT and PP analyses were performed on all variables. 	<ol style="list-style-type: none"> 1. The study was inadequately powered to prevent a type II error. 2. Despite randomization, there were significant baseline differences between the treatment groups with respect to baseline WHO functional status, QOL scores, and proportion of post-PEA patients. This made it difficult to draw conclusions from end-of-study differences in these parameters across study groups. 3. Subgroup analysis was not conducted to investigate differences in response to the therapy among newly diagnosed CTEPH patients and post-PEA patients with persistent or recurrent PH.
Surie, ⁵ 2013	<ol style="list-style-type: none"> 1. The treatment groups were well matched with respect to baseline hemodynamic severity of disease and the degree of RV dysfunction and remodeling. 2. To minimize possible observer bias all observers were blinded toward the treatment regimen and 	<ol style="list-style-type: none"> 1. Though randomized, the study was open-label. However, it is unlikely that the outcomes with regards to pulmonary remodeling may have been impacted. 2. This was a sub-study with an outcome which the original study was not designed to detect, and it was inadequately powered to detect its specified outcome.

First Author, Publication year	Strengths	Limitations
	each cMRI parameter was analyzed by the same observer in all patients to avoid inter-observer variation.	
6-MWD = 6 minute walking distance; CTEPH = chronic thromboembolic pulmonary hypertension; cMRI = cardiac magnetic resonance imaging; ITT = intention-to-treat; PEA = pulmonary endarterectomy; PH = pulmonary hypertension; PP = per-protocol; RCT = randomized controlled trial; QOL = quality of life; WHO = World Health Organization		

Appendix 4: Main Study Findings and Authors' Conclusions

First Author, Publication year	Main Study Findings	Authors' Conclusions
Becattini, ⁶ 2010	<ol style="list-style-type: none"> 1. Three-to- six month bosentan therapy showed a significant improvement in the 6-MWD, especially in the non-randomized studies. 2. Consistent hemodynamic improvements were observed in open-label and controlled studies. 3. Data from this systematic review suggest that there might be a greater efficacy of bosentan therapy in inoperable CTEPH patients than in persistent PH after PEA patients. 	"In conclusion, our data suggest a potential role of bosentan therapy in the treatment of CTEPH that need confirmation in controlled clinical studies." ⁶ Page e56
Ghofrani, ⁴ 2013	<ol style="list-style-type: none"> 1. The least-squares mean difference in 6-MWD between the riociguat and placebo groups was 46 meters at 16 weeks in favor of riociguat (95% CI: 25 to 67; $P < 0.001$). 2. The least-squares mean difference in the reduction of PVR between the riociguat and placebo groups was $-246 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$ at 16 weeks in favor of riociguat; 95% CI: -303 to -190; $P < 0.001$). 	"Riociguat significantly improved exercise capacity and pulmonary vascular resistance in patients with chronic thromboembolic pulmonary hypertension." ⁴ Page 319
Reesink, ¹ 2010	<ol style="list-style-type: none"> 1. At 16 weeks, bosentan treatment was associated with a significant decrease in TPR whereas the no-bosentan group showed a small, but non-significant increase in TPR. The mean difference between the change in the groups was $299 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$ (95% CI: 105 to 493; $P = 0.004$). 2. After the PEA, the duration of stay in the intensive care unit and the duration of mechanical ventilation use showed no significant difference between the bosentan and no-bosentan groups. 3. Number of deaths during or after PEA was lower in the bosentan group ($n = 1$) compared with the no-bosentan group ($n = 3$). 	"Patients with proximal chronic thromboembolic pulmonary hypertension may benefit hemodynamically and clinically from treatment with bosentan before pulmonary endarterectomy. Individual factors predictive of a beneficial response and whether this influences either morbidity or mortality associated with pulmonary endarterectomy remain to be established." ¹ Page 85
Suntharalingam, ⁷ 2008	<ol style="list-style-type: none"> 1. Although the sildenafil group achieved improvements in 6-MWD score at 12 weeks, the difference did not reach a statistical significance. 2. Compared to placebo, sildenafil significantly improved WHO functional class and PVR in patients with distal CTEPH over 12 weeks. 3. There was a significant improvement within the sildenafil group in the activity domain of CAMPHOR score of QOL assessment at 12 weeks. However, disparities at baseline between the groups in this respect make it difficult to draw 	"In conclusion, although this study was insufficiently powered to test the primary endpoint, it did suggest beneficial effects in favor of sildenafil in several secondary endpoints. Although PEA remains the treatment of choice for CTEPH, this treatment offers a new potential therapeutic option for those in whom surgery is not possible." ⁷ page 235

First Author, Publication year	Main Study Findings	Authors' Conclusions
Surie, ⁵ 2013	<p>conclusions.</p> <ol style="list-style-type: none"> Both RV and LV systolic functions increased modestly in the bosentan treated group whereas patients in the control group experienced worsening systolic function. Consequently the change from baseline for the two groups in all systolic function parameters differed significantly in favor of bosentan. RV mass decreased significantly in the bosentan group but increased in the no-bosentan group. Thus, the changes from baseline in RV remodeling differed significantly between the bosentan-treated and the no-bosentan groups. LV mass remained unchanged in both groups after 16 weeks. Pulmonary hemodynamics improved in the bosentan group but not significantly. In contrast, patients in the control group exhibited worsening of their hemodynamic values. 	<p>"In patients with operable CTEPH, compared with best standard of care, active treatment with bosentan for 16 weeks was associated with significant improvements in RV function and remodeling."⁵ page 703</p>
<p>6-MWD = 6 minute walking distance; CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; QOL = quality-of-life; LV = left ventricular; mPAP = mean pulmonary artery pressure; PEA = pulmonary endarterectomy; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; TPR = total pulmonary resistance; RCT = randomized controlled trial; RV = right ventricular; WHO = World Health Organization</p>		